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POSITRON-EMITTING RADIOLIGANDS FOR IMAGING NEUROLEPTIC RECEPTORS.

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A series of ^{18}F-labeled butyrophenone neuroleptics was evaluated in baboons and rats with respect to potential utility as radioligands for studying neuroleptic receptors in the living human brain by positron emission tomography (PET). The series included benperidol, haloperidol, spiroperidol, and N-methylspiroperidol. The criteria used for the evaluation were: 1) a rapid radiochemical synthesis and purification, 2) a high specific activity product, 3) a rapid and significant brain penetration, 4) minimal radioactive metabolites within the brain during the scanning period, 5) a high degree of specificity of receptor binding, and 6) a relatively slow *in vivo* dissociation from the receptor once bound (1).

The first two criteria were met for all four compounds with the development of a general synthesis (2) for butyrophenones radiolabeled with fluorine-18 to specific activities greater than 10 Ci/μmol, calculated to the end of cyclotron bombardment (3). These compounds were administered to baboons, and the radioactivity distributions to the striatum, a region of high receptor concentration, and to the cerebellum, a region of low receptor concentration, were determined by PET at various times up to 6 hours after isotope injection (1,4). Stereospecific binding to neuroleptic receptors was demonstrated in the striatum but not in the cerebellum by comparing studies in the same animal pretreated with either (-)- or (+)-butaclamol. Among the radioligands studied, [^{18}F]benperidol, [^{18}F]spiroperidol, and [^{18}F]-N-methylspiroperidol exhibited appropriate *in vivo* stereospecific binding kinetics to be useful for studying neuroleptic receptors. Analysis of baboon blood for radioactive metabolites indicates a rapid peripheral metabolism for these compounds. However, the very long retention of radioactivity in the striatum suggests that very little metabolism takes place in the central nervous system. Analysis of rat brain at various tim after injection of [^{18}F]spiroperidol or [^{18}F]-N-methylspiroperidol demonstrated that greater than 95% of the radioactivity in the striatum was due to unchanged radioligand for as long as 4 hours after injection. The absolute striatal uptake (in percent of administered dose) in the baboon was at least two-fold higher for [^{18}F]-N-methylspiroperidol than for [^{18}F]spiroperidol. In the rat, the striatal uptake was five-fold higher for the N-methyl radioligand.

Although [^{18}F]haloperidol exhibited a higher initial brain uptake than the other three, the distribution of radioactivity was predominantly to nonspecific sites, and the striatal retention was much less than for the other compounds. [^{18}F]Benperidol, [^{18}F]spiroperidol, and [^{18}F]-N-methylspiroperidol all showed a high percentage of specifically bound component of radioactivity in the baboon striatum which increased for the duration of the study. At 4 hours after injection, the striatum to cerebellum ratios for these three compounds were 7.3, 3.4, and 8.0, respectively, whereas for [^{18}F]haloperidol the corresponding ratio was 1.6. [^{18}F]Spiroperidol exhibited a higher initial distribution to cortical areas than either [^{18}F]benperidol or [^{18}F]-N-methylspiroperidol, suggesting a lower specificity with perhaps a higher proportion of binding to serotonin receptors in these regions, as has been found for [^{3}H]spiroperidol. These results indicate that [^{18}F]-N-methylspiroperidol, because of its high brain uptake,

specific distribution to neuroleptic receptors, insignificant metabolism in the central nervous system, and slow dissociation rate, is an ideal choice for PET studies of neuroleptic receptors in humans. We have recently confirmed this positive evaluation by performing human studies with this compound. PET studies for as long as 12 hours after injection suggest that this compound binds irreversibly *in vivo* to sites in the human caudate-putamen.

A model was developed which allows the determination of association and dissociation rate constants for specific binding. The *in vivo* kinetics of this binding differed significantly from the kinetics of specific binding of the same compounds studied *in vitro*. By using this model and varying the specific activity of the radioligand administered, the concentration of neuroleptic receptors in various brain regions may be determined *in vivo*.

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